REMARKS

A. Status of the Claims

Claims 3-19 are pending in the application. Claims 3-6 and 13-19 were examined in the Office Action mailed January 4, 2007. Claims 7-12 stand withdrawn. New claim 20 has been added. Pursuant to 37 CFR 1.116, Applicant urges that claim 20 should be entered by the Examiner because it places the application in condition for allowance or in better form for appeal. None of the prior art identified by the Examiner anticipates or renders obvious claims to methods of treating acne rosacea, such as that presented in claim 20. Claim 20 finds support, for example, in originally filed claim 3.

B. The Pending Claims Are Patentable Over Bernstein

The Action rejected claims 3, 5-6, and 13-19 under 35 U.S.C. § 103(a) as *prima facie* obvious over U.S. Pat. No. 4,505,896 to Bernstein ("Bernstein"). The Action asserts that one would have been motivated by Bernstein to expect the claimed compositions to be effective because Bernstein suggests the combination of nicotinic acid and nicotinamide. Applicant has previously asserted – and continues to assert – that Bernstein does not, in fact, suggest the combination of nicotinic acid and nicotinamide. Those arguments are of record and will not be repeated in the present reply. Applicant, however, submits the following further arguments which independently overcome the rejection.

1. *The Rejection does not properly ascertain the differences between the claimed invention and the prior art*

In making these rejections, the Action fails to consider both the invention and the prior art as a whole (See MPEP 2141.02), and has instead merely pointed out that nicotinic acid or nicotinamide were previously used in the treatment of acne vulgaris. The Examiner has

completely ignored the criticality of the relative concentrations and combination of the two ingredients for the treatment of acne vulgaris or acne rosacea. The Action has thus failed to make a *prima facie* case of obviousness.

Further, the Action misapplies In re *Aller* saying that "[w]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation" and thus a *per se* bar to patentability of any modification of the teachings of Bernstein. Yet according to In re *Ochiai*, there are no *per se* rules when determining obviousness under 35 USC § 103. "The use of *per se* rules, while undoubtedly less laborious than a searching comparison of the claimed invention – including all its limitations – with the teachings of the prior art, flouts section 103 and the fundamental case law applying it." In re Ochiai, 71 F3d 1565, 1572 (Fed. Cir. 1995).

Finally, the Action also does not fully address the standards for patentability explained by the Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966) and as cited in MPEP 2141, which states that these guidelines are to be applied in <u>each and every case</u>. Patentability is determined by:

A) Determining the scope and content of the prior art;

B) Ascertaining the differences between the prior art and the claims in issue;

C) Resolving the level of ordinary skill in the art; and

D) Evaluating objective evidence of non-obviousness.

In the present case, the Action does not properly ascertain the differences between the prior art and the claims in issue.

Bernstein discloses only that nicotinic acid and nicotinamide are interchangeable for the treatment of acne vulgaris. At no point does Bernstein disclose any indication that nicotinamide

or nicotinic acid are in any way preferable one over the other. Throughout Bernstein, nicotinamide and nicotinic acid are presented as having equivalent efficacy. The recommended concentration ranges are the same for both. Examples 9, 11, 13 and 14 claim to have tested topical solutions of nicotinic acid **or** nicotinamide and found both effective. No disparities in their relative effectiveness were noted anywhere in the reference. Thus, based on the disclosure of Bernstein, one skilled in the art would have reasonably assumed that nicotinic acid and nicotinamide were entirely interchangeable in topical acne treatments.

Bernstein also only discloses effective amounts of nicotinamide or nicotinic acid of 1.0% or greater and implicitly suggests that the recommended concentration ranges for both active ingredients are the same. Bernstein does not disclose using amounts of nicotinic acid less than about 0.7%. Bernstein does not disclose using 2.0% or greater nicotinamide with less than 0.7% nicotinic acids.

Bernstein does not recognize the problem of providing an effective skin treatment for acne vulgaris that limits skin irritation. Furthermore, Bernstein does not disclose treatments of acne rosacea at all. **All these differences between the present invention and Bernstein are dismissed or ignored by the Action.**

The Action dismisses the fact that Bernstein does not disclose using amounts of nicotinic acid less than 0.7% by arguing that:

> With regard to the claimed range of about 0.005-0.7% in claim 3, Bernstein teaches the use of nicotinic acid in the amount of 1% and it is the examiner's position that 1% renders about 0.7% obvious. Applicant has not defined 'about' in the specification to mean exact. . . Further, the manipulation of this concentration is considered obvious absence unexpectedness of the instantly claimed amount of 0.7% versus 1%. 'Generally, differences in concentration or temperature will not support the patentability of the subject matter encompassed by the prior art unless there is evidence indicating that such concentration or temperature is critical. [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

> experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Office Action at p. 3.

The Action does not properly interpret the meaning of the phrase "about 0.7%." The term is not without meaning merely because the "Applicant has not defined 'about' in the specification to mean exact." The Federal Circuit has recently offered detailed instruction as to how claims using the word "about" are to be interpreted:

> This court has looked at the meaning of the term "about," and similar qualifying words or phrases, in other cases and has developed an approach to the interpretation of such terms:
>
> > [T]he word "about" does not have a universal meaning in patent claims . . . the meaning depends upon the technological facts of the particular case.
> > ***
> > The use of the word "about," avoids a strict numerical boundary to the specified parameter. Its range must be interpreted in its technological and stylistic context. **We thus consider how the term . . . was used in the patent specification, the prosecution history, and other claims. It is appropriate to consider the effects of varying the parameter, for the inventor's intended meaning is relevant.** Extrinsic evidence of meaning and usage in the art may be helpful in determining the criticality of the parameter . . .
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> *Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995)(citations omitted). *See also Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1554 (Fed. Cir. 1996)(stating that "the usage [of the term 'about'] can usually be understood in light of the technology embodied by the invention"); *Conopco, Inc. v. May Dep't Stores Co.*, 46 F.3d 1556 (Fed. Cir. 1994)(discussing the criticality of the claimed ratio to the invention and whether or not one of ordinary skill in the art would have read the modifier "about" expansively in light of the **intrinsic evidence**.)
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> *Ortho-McNeil Pharmaceutical, Inc. v. Caraco Pharmaceutical Laboratories, Ltd.*, 476 F.3d 1321, 1327-8 (Fed. Cir. 2007)

The proper analysis therefore must interpret the meaning of "about 0.005-0.7 % in its technological and stylistic context. It is therefore critical that one consider how the term is used

in the patent specification and evidence of the inventor's intended meaning. Turning to the specification, one finds the following passage:

> "Clinical studies with nicotinamide involving over one thousand acne patients performed by myself or by colleagues under my supervision over the last twenty years have demonstrated that topical nicotinamide is modestly effective when compared to placebo in treating acne vulgaris or acne rosacea. However, I have found that nicotinic acid is too irritating to be applied topically on a continuous or regular basis at the concentrations (1.0% to 10%) claimed in my 4,505,896 patent [Bernstein]." (Specification at pargraph 4).

The inventor's clear intent here is to express that formulations containing the same concentrations of nicotinic acid disclosed in the Bernstein reference are explicitly outside the scope of his invention. Thus it is clear that "about 0.7%" in the present claims are not defined as or intended to encompass values of nicotinic acid disclosed in Bernstein. The term must be interpreted in that context. **Thus it is plain that the range "about 0.005-0.7 %" falls outside the effective ranges taught by Bernstein.**

The Action continues it's argument with regard to the lack of substantial differences between Bernstein and the present invention by quoting the following:

> Generally, differences in concentration or temperature will not support the patentability of the subject matter encompassed by the prior art unless there is evidence indicating that such concentration or temperature is critical. [W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Office Action at p. 3.

In this case the claimed concentrations **are** critical, and are therefore patentable over the prior art. Bernstein only discloses that amounts of nicotinamide and nicotinic acid ranging from 1 to 10% in concentration are effective. The present invention therefore falls outside the ranges taught by Bernstein with regard to nicotinic acid concentration. And even if Bernstein is read as encompassing formulations containing both nicotinic acid and nicotinamide (which it does not) Bernstein discloses that nicotinic acid and nicotinamide are functionally equivalent and thus one

skilled in the art would have understood from Bernstein that the relative concentrations of the two ingredients was not critical so long as the prescribed concentration range was reached.

In contrast, the present invention has identified that it is critical that the amount of nicotinamide be greater or equal to about 2.0% and that the nicotinic acid concentration was less than about 0.7% to achieve effective treatment of acne vulgaris or acne rosacea while minimizing skin irritation.

For these reasons, the Action does not make a *prima facie* case of obviousness, and Applicant respectfully requests that these rejections be withdrawn.

2. The Action provides no adequate rationale to support the rejection under 35 U.S.C. §103

The Action provides no teaching, no suggestion, nor any other rationale why one of ordinary skill in the art would be motivated to combine the claimed ingredients at the claimed concentrations. Nor has the Action pointed to any evidence of a reasonable expectation by one skilled in the art that a relatively small amount of nicotinic acid would successfully make a nicotinamide formulation substantially more effective than one otherwise would predict. Without such a rationale, the Action fails to make a *prima facie* case of obviousness.

The Action argues that "one would have been motivated to do so with a reasonable expectation of success since Bernstein suggests the combination of nicotinic acid and nicotinamide." The problem with this assertion is that it does not take into account the degree of success, which is what is at issue. Applicant does not dispute that the nicotinic acid or nicotinamide formulations disclosed by Bernstein are moderately effective at treating acne vulgaris. But Applicant directly compared a prior art Bernstein formulation and a claimed

formulation in Example 3 of the specification. Those experimental results showed the prior art formulation to be entirely ineffective for the patient and the claimed formulation to be entirely effective. **The Action provides no rationale whatsoever as to why one skilled in the art would have reasonably expected or predicted that result.**

Without any rationale and without any evidence that the disclosed results would be predictable, or that the claimed combination would have a reasonable expectation of success to the degree demonstrated by the Applicant, the Action fails to make a *prima facie* case of obviousness.

For these reasons, the Action does not make a *prima facie* case of obviousness, and Applicant respectfully requests that these rejections be withdrawn.

3. The Action disregards Applicant's evidence of unexpected and surprising results

The Action disputes that results disclosed in the specification are surprising and unexpected, stating that:

> A greater than additive effect is not necessarily sufficient to overcome a *prima facie* case of obviousness because such an effect can be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage." (Office Action at p. 4)(emphasis added)

The Action further argues that "applicant's examples do not provide any data for the examiner to determine if merely an additive effect is seen or a synergistic effect." Applicant strongly disputes this determination.

Example 3 of the present specification discloses that 4.0% nicotinamide solution was entirely ineffective for treating a patient's acne lesions, but an addition of 0.05% nicotinic acid to the nicotinamide solution resulted in a composition that cleared the patient's acne lesions

completely. Obviously, it is difficult to put precise numbers on the treatment of biological conditions such as acne vulgaris, but given Bernstein's disclosure that nicotinamide and nicotinic acid are entirely interchangeable, what is disclosed in Example 3 can only be described as a startling result. The 0.05% nicotinic acid is by weight $1/80^{th}$ the amount of nicotinamide in the preparation. Thus this result cannot be dismissed as merely additive or somehow within the range of results one skilled in the art would reasonably have expected or predicted. **One skilled in the art would not have expected, based on the prior art, that such a small addition of nicotinic acid would result in any measurable effect, much less a complete change in treatment outcome.** The Action makes no reasonable or adequately supported argument otherwise.

Finally, the Action asserts that "[i]f arguendo applicant can show a synergistic action . . . the examiner points out that the claims are not commensurate in scope." Office Action at p. 5. Applicant disputes this assertion. Examples 1 and 3, demonstrate that the addition of 0.05% or 0.1% nicotinic acid leads to effective treatment of acne vulgaris when added to a nicotinamide formulation. Example 2 shows that addition of 0.05% of nicotinic acid to a nicotinamide formulation was effective for treating acne rosacea. First of all, it is Applicant's assertion that 0.05% and 0.1% are fairly representative of the range "about 0.05 to 0.7%." Secondly, it is reasonable to expect that if application of the minimal amount of nicotinic acid is effective, then application of additional amounts will also be effective, albeit increasingly irritating to the skin. Thus it is the Applicant's assertion that the claimed ranges are fully commensurate with the evidence of unexpected results presented in the specification.

For these reasons, the Action both fails to make a *prima facie* case of obviousness or, to the extent that any *prima facie* case is made, that case is fully rebutted by Applicant's evidence of

surprising and unexpected results. Applicant therefore respectfully requests that these rejections be withdrawn.

B. The Pending Claims Are Patentable Over Bernstein in View of Scivoletto I

The Action rejects claim 4 under 35 U.S.C. § 103(a) as *prima facie* obvious over U.S. Pat. No. 4,505,896 to Bernstein in view of U.S. Pat. No. 6,248,763 ("Scivoletto I"). The Action asserts that Bernstein does not teach about 0.05-0.2% nicotinic acid, but that Scivoletto I "teaches a composition comprising nicotinic acid, nicotinamide, and nicotinic esters as the active ingredient to treat skin disorders including acne."

1. The Rejection does not properly ascertain the differences between the claimed invention and the prior art

As discussed above, to make a *prima facie* case of obviousness the rejection must consider the differences between the claimed invention and the prior art. Those differences are discussed above with regard to Bernstein.

The Action acknowledges Scivoletto I does not teach a combination of nicotinic acid and nicotinamide. But further, Scivoletto I only discloses methods of treating acne which require the use of glycolic acid. Glycolic acid is present either in a single composition applied to acne lesions (Scivoletto I, col. 2, ln. 50 to col. 3., ln. 3) or in one of a pair of compositions applied to the lesions (Scivoletto I, col. 3, lns. 16-30). The reason for this is reportedly because the glycolic acid "acts as an exfoliant, and it peels away the unwanted material." Scivoletto I does not appear to disclose any method of acne treatment that does not incorporate the use of a glycolic acid

peeling step nor does it teach or suggest that the compositions not containing glycolic acid will be effective for the treatment of acne without the initial peeling step.

Additionally, although Scivoletto I only does not explicitly state what type of acne it is treating, when read as a whole it is likely that "acne" in Scivoletto I refers to acne vulgaris, since there are references to "acne blemishes" and "acne pimples" (Scivoletto I, col. 3, lns. 31-3) but not to the flushing and blood vessel dilation typical of acne rosacea. Thus, Scivoletto I also fails to disclose treatments of acne rosacea.

Scivoletto I, therefore, differs from the prior art in that it does not disclose a combination of nicotinic acid and nicotinamide, in that it requires that the acne lesions be treated with the active ingredient glycolic acid and exfoliated (and therefore strongly irritated) in order to provide effective treatment of acne vulgaris. This is apparently why Scivoletto I indicates that its acne treatment containing glycolic acid is to be "applied twice daily for 2 to 3 days" rather than continuously or on a regular basis.

Furthermore, Scivoletto I does not disclose any method of treating acne rosacea.

The Action asserts that Bernstein rescues Scivoletto I's failure to disclose combinations of nicotinic acid and nicotinamide. Applicant respectfully disputes this. As discussed above, Bernstein does not disclose combining nicotinic acid and nicotinamide at the claimed concentrations. At most Bernstein suggests that the two are interchangeable. While Scivoletto I discloses formulations containing nicotinic acid in the claimed ranges, replacing that nicotinic acid with nicotinamide (as might arguably be suggested by Bernstein) still does not yield compositions within the claimed ranges. Thus there is still a large gap between the asserted prior art combination and the present invention.

For these reasons, the Action does not make a *prima facie* case of obviousness, and Applicant respectfully requests that this rejection be withdrawn.

2. The Action provides no adequate rationale to support the rejection under 35 U.S.C. §103

Again, the Action provides no teaching, no suggestion, nor any other rationale why one of ordinary skill in the art would be motivated to combine the claimed ingredients at the claimed concentrations other than to say that Scivoletto I "teaches nicotinic acid for the treatment of acne in the amount of 0.01-1%." Office Action at p. 6. This is a misstatement of what Scivoletto I teaches. Scivoletto I teaches compositions for the treatment of acne that contain a number of ingredients in addition to nicotinic acid, including glycolic acid, methyl nicotinate, aloe vera gel, glycerin, vitamin E and others. Scivoletto I expressly states that "[i]n the following preferred embodiments, the **active ingredient** listed is methyl nicotinate." (Col. 2, lns. 45-49.) In the preferred embodiment "intended to treat acne" Scivoletto I discloses a specific composition that includes a combination of 0.01 to 1% methyl nicotinate and 0.01 to 1% nicotinic acid. (Col. 2, lns. 44-64). Scivoletto's disclosure is narrowly drawn and only fully enables the methyl nicotinate/nicotinic acid in combination with "a skin moisturizer, a suitable carrier, an emollient (e.g. glycerol or glycerin), vitamin E and other elements and excipients." (Col. 2, lns. 12-15.) It does not adequately describe or enable any other combinations, nor does it suggest that 0.01-1% nicotinic acid by itself is an effective treatment for acne vulgaris.

Thus the Action has not pointed to any viable rationale as to why one would select the nicotinic acid component of the formulation disclosed in Scivoletto I – and only that component

– for combination with the nicotinamide formulations of Bernstein to produce an acne treatment that is surprisingly more effective than Bernstein alone.

For these reasons, the Action does not make a *prima facie* case of obviousness, and Applicant respectfully requests that this rejection be withdrawn.

3. The Action disregards Applicant's evidence of unexpected and surprising results

Again, nothing in the combination of Scivoletto I and Bernstein makes the results reported by Applicant anything other than surprising or unexpected. One of ordinary skill in the art could not have predicted based on the combined teachings of Scivoletto I and Bernstein that the claimed formulations would be so much more effective than Bernstein's formulations alone.

For these reasons, the Action both fails to make a *prima facie* case of obviousness or, to the extent that any *prima facie* case is made, that case is rebutted by Applicant's evidence of surprising and unexpected results. Applicant therefore respectfully requests that these rejections be withdrawn.

C. The Pending Claims Are Patentable Over Bernstein in View of Scivoletto II

The Action rejects claims 3-6, 13-17, 19 under 35 U.S.C. § 103(a) as *prima facie* obvious over U.S. Pat. No. 6,429,218 ("Scivoletto II") in view of Bernstein (4,505,896). The Action asserts that Scivoletto II is teaches formulating nicotinic acid (niacin), amide or ester in a lotion, cream or serum with a desired percentage and also package small ampoules containing niacin (nicotinic acid) to increase the concentration of nicotinic acid in the base formulation. The Action also asserts that Scivoletto II teaches the method of shrinking pimples, but does not specifically teach the treatment of acne vulgaris.

1. *The Rejection does not properly ascertain the differences between the claimed invention and the prior art*

The Action does not fully consider the teachings of Scivoletto II. Throughout Scivoletto II it is clear that the active ingredient (nicotinic acid) is present to produce "warmth, flushing or redness which may last from 15 to 30 minutes." (Col. 1, lns. 19-21.) While the patent discloses that "Applicant has found that skin flushing and reddening adds to the effect of reducing enlarged pores, minimizing fine lines, penetration of moisturizer ingredients, shrinking of pimples, removal of blackheads or other unwanted dirt or oxidents [*sic*] under the skin, tightening of the skin due to the flushing and topical circulation of the reddening" (Col. 2, lns. 14-19) it is not apparent that these are any more than temporary, cosmetic effects. Indeed, as the Action admits (Office Action at p. 7), this teaching is not clearly a teaching of a treatment for acne. In contrast, the application mentions the treatment of acne **specifically** at only one place in the disclosure, saying: "[i]n all formulas other active ingredients for **other** skin conditions such as **acne** or psoriasis may be used. Such active ingredients may be glycolic acid, resorcinol monacetate, saliciylic acid and witch hazel." In this portion of the specification the clear implication is that the formulations and active ingredients previously disclosed are not necessarily effective for acne specifically, and that the active ingredients appropriate for acne do not explicitly include nicotinic acid or nicotinamide. Scivoletto II therefore does not teach or suggest nicotinic acid or nicotinamide as an active ingredient for the treatment of acne, but instead only for temporarily creating red or flushed skin.

Nor is it proper to assume that "a skilled artisan would have reasonably expected success since Scivoletto teaches the composition is effective in shrinking pimples, a symptom of acne. . . " (Office Action at p. 8) Pimples can be symptoms of a number of skin diseases including

bacterial skin infections such as those from *Staphylococcus aureus* (*e.g.* impetigo), viral skin infections such as molluscum contagiosum and various fungal infections. Pimples are thus in no way unique to acne vulgaris. The Action presents no reasonable rationale as to why one skilled in the art would reasonably expect that a treatment for "pimples" would be effective regardless of the etiology of those skin lesions.

Scivoletto II also does not appear to disclose any methods of treating acne rosacea.

For these reasons, the Action does not make a *prima facie* case of obviousness, and Applicant respectfully requests that these rejections be withdrawn.

2. The Action provides no adequate rationale to support the rejection under 35 U.S.C. §103 over Scivoletto II in view of Bernstein

The Action argues that it would have been obvious to combine the teachings of Scivoletto II and Bernstein to treat acne vulgaris. One would be motivated to do so, it asserts, because Bernstein teaches nicotinamide and nicotinic acid are effective in treating acne vulgaris and that "a skilled artisan would have reasonably expected success since Scivoletto teaches the composition is effective in shrinking pimples, a symptom of acne, and active ingredients for treating skin disorders such as acne may also be utilized." Office Action at p. 7-8.

Applicant respectfully disputes the Actions assertion that there would be motivation to combine these two references. First, it is not apparent that Scivoletto II discloses anything more than temporarily improve the appearance of pimples and blackheads. Indeed, the disclosure regarding acne later in the disclosure indicates that Scivoletto II believed that treatment of acne required entirely different active ingredients, active ingredients that **do not include** nicotinic acid or nicotinamide. Therefore, based on the prior art one of ordinary skill would have no

motivation to believe that combining Scivoletto II with Bernstein would do anything more than produce a temporary cosmetic improvement of the acne's appearance, one that disappeared 15 to 30 minutes later along with the redness. **Indeed, based on Scivoletto II explicit teachings one of ordinary skill would have predicted that additional ingredients such as glycolic acid would be required to produce an effective acne treatment.** Nothing in Scivoletto II suggests that the nicotinamide formulations of Bernstein can be substantially improved for use in acne-treatment methods merely by the addition of small amounts of nicotinic acid. Nor does Bernstein in any way suggest that the addition of reddening agents would improve its formulations.

For these reasons, the Action does not make a *prima facie* case of obviousness, and Applicant respectfully requests that these rejections be withdrawn.

3. The Action disregards Applicant's evidence of unexpected and surprising results

Once again, nothing in the combination of Scivoletto II and Bernstein makes the results reported by Applicant anything other than surprising or unexpected. One of ordinary skill in the art could not have predicted based on the combined teachings of Scivoletto II and Bernstein that the claimed formulations would be so much more effective than Bernstein's formulations alone at treating acne.

For these reasons, the Action both fails to make a *prima facie* case of obviousness or, to the extent that any *prima facie* case is made, that case is rebutted by Applicant's evidence of surprising and unexpected results. Applicant therefore respectfully requests that these rejections be withdrawn.

CONCLUSION

Applicant respectfully submits that, in light of the preceding discussion and amendments, the present claims are in condition for allowance, and further respectfully requests that all rejections over Bernstein, Scivoletto, and Scivoletto II, be withdrawn. If the Examiner has any questions or suggestions that might expedite the allowance of the pending claims, a telephone call to Applicant's representative Tim Corder at 512.542.8446 would be welcomed.

Respectfully submitted,

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